

## **PSJ2 Exh 104**

**File Provided Natively**



# ENDO PHARMACEUTICALS




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**Awakening to REMS... *A New Reality in Pain Management***  
R&D Lunch & Learn  
November 15, 2011

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## AGENDA



- What is REMS- *Tara Chapman*
- Endo's FDA-approved Risk Minimization Activities- *Mark Collins*
- Public Health Issue Associated with Opioid Use- *Nancy Santilli*
- REMS Education & Resources- *Linda Kitlinski*
- Q & A

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## WHAT IS REMS?

- REMS – RISK EVALUATION AND MITIGATION STRATEGY
- REMS are part of certain drug and biologics applications to ensure the benefits of the drug (NDA/ANDA) or biologic (BLA) would outweigh the risks.
- The FDA may require that a REMS include elements that are necessary to assure safe use of the drug/biologic because of its inherent toxicity or potential harmfulness, if it is determined that:
  - The drug/biologic is shown to be effective but is associated with a serious adverse drug experience. The REMS is strategy to mitigate specific serious risk listed in the labeling for the drug/biologic
  - FDA is also authorized to require sponsors of approved applications without a REMS to submit a proposed REMS if the FDA becomes aware of new safety information

## REMS BACKGROUND

- FDAAA – FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007
  - Signed into Law September 27, 2007
- To ensure industry compliance regarding REMS, civil money penalties can be applied for sponsor's violation to the requirement for a REMS
- The drug/biologic will be considered misbranded if the sponsor fails to comply with a requirement of the REMS.

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## REMS VS. RISKMAP

- Required versus Recommended
- Content comparison using the Opana ER RiskMAP as an example
  - Submission of Assessments
  - Additional potential elements of the strategy (MedGuide and PPI)
  - Communication Plan
  - ETASU
  - Implementation System

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## ENDO'S READINESS: CURRENT FDA-APPROVED RISK MINIMIZATION ACTIVITIES FOR ENDO'S PRODUCTS

- RiskMAP – the forerunner to REMS
- Several of our products have Medication Guides
  - Required if the FDA determines that the drug product is:
    1. one for which patient labeling could help **prevent** serious adverse effects
    2. one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could **affect patients' decision** to use, or to continue to use, the product
    3. important to health and patient adherence to directions for use is **crucial to the drug's effectiveness**

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|--|---|----------|--------------|---------------------------|
| CURRENT AND FUTURE FDA-APPROVED RISK MINIMIZATION ACTIVITIES# FOR ENDO'S PRODUCTS                |   |          |              |                           |
| Class/Product  | Current FDA-approved Risk Minimization Activities |          |              | REMS in Prep?             |
|  | Med Guide (MG)                                    | RiskMAP  | REMS         |                           |
| Antidepressants<br>Amitriptyline HCl tablets<br>Trazodone HCl tablets<br>Venlafaxine HCl tablets | ✓   |          |              |                           |
| Aveed*   | –   | –        | –            | ✓                         |
| Clonazepam tablets   | ✓   |          | ✓ (MG only)  |                           |
| Fentanyl generic*  | –   | –        | –            | ✓                         |
| Fortesta   | ✓   |          |              |                           |
| NSAIDs   | ✓   |          |              |                           |
| Levetiracetam tablets  | ✓   |          | Not any more |                           |
| Metoclopramide tablets   | ✓   |          | Not any more |                           |
| Morphine sulfate ER  |   |          |              | ✓                         |
| Mycophenolate  | ✓   |          |              | ✓                         |
| Opana ER   |   | ✓        |              | ✓                         |
| Oxycodone HCl ER   |   |          |              | ✓                         |
| Primidone tablets  | ✓   |          | Not any more |                           |
| Propoxyphene(s)  | ✓   |          | ✓ (MG only)  |                           |
| Voltaren Gel   | ✓   |          |              |                           |
| Zolpidem tartrate tablets  | ✓   |          | Not any more |                           |
| <b>Totals</b>  | <b>11</b>   | <b>1</b> | <b>2</b>     | <b>6 Products; 4 REMS</b> |

\* Unapproved

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\* Not including Patient Labeling (required for products containing estrogen)

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|---|---|--|
| ENDO'S READINESS: PARTICIPATION IN CLASS-WIDE REMS FOR PAIN PRODUCTS  |   |  |
| Products(s)   | Opana ER<br>Oxycodone HCl ER<br>Morphine sulfate ER   | Actiq generic<br>(fentanyl)  |
| Class   | Long Acting / Extended Release (LAER) Opioids<br>(21 Companies)   | Transmucosal Immediate Release Fentanyl (TIRF)<br>(10 Companies)   |
| ETASUs  | 1. HCP training program<br>2. Patient education materials<br>3. HCP notification  | 1. HCPs specially certified<br>2. Specially certified pharmacies<br>3. Dispensed only with evidence of safe-use conditions   |
| About the REMS program  | The Sponsors will ensure that <b>training is provided</b> to healthcare providers who prescribe ER/LA opioids. The training will be conducted by <b>accredited, independent continuing education (CE) providers</b> , under educational grant provided by the Sponsors. Assessments of the <b>effect of the CE program</b> will be provided to the FDA. | <b>Access to these medicines will be restricted</b> to appropriately trained distributors, pharmacists, prescribers, and patients. Access requires <b>successful completion of Knowledge Assessment</b> . Entities re-enrolled every 2 years. Major assessments provided to the FDA: <b>operational metrics</b> of the REMS. |
| Expected REMS approval  | Class REMS: February 2012<br>Interim REMS: December 2011  | Class REMS: December 2011<br>Endo's ANDA: 4Q2012   |

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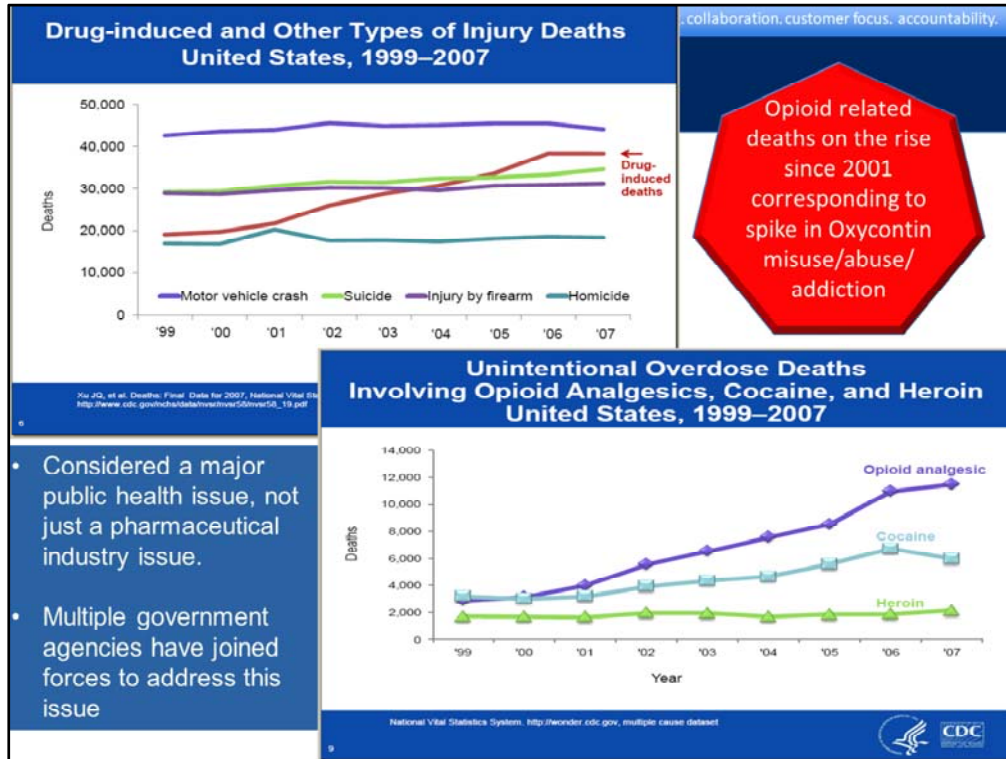
## PUBLIC HEALTH ISSUE OF OPIOID USE

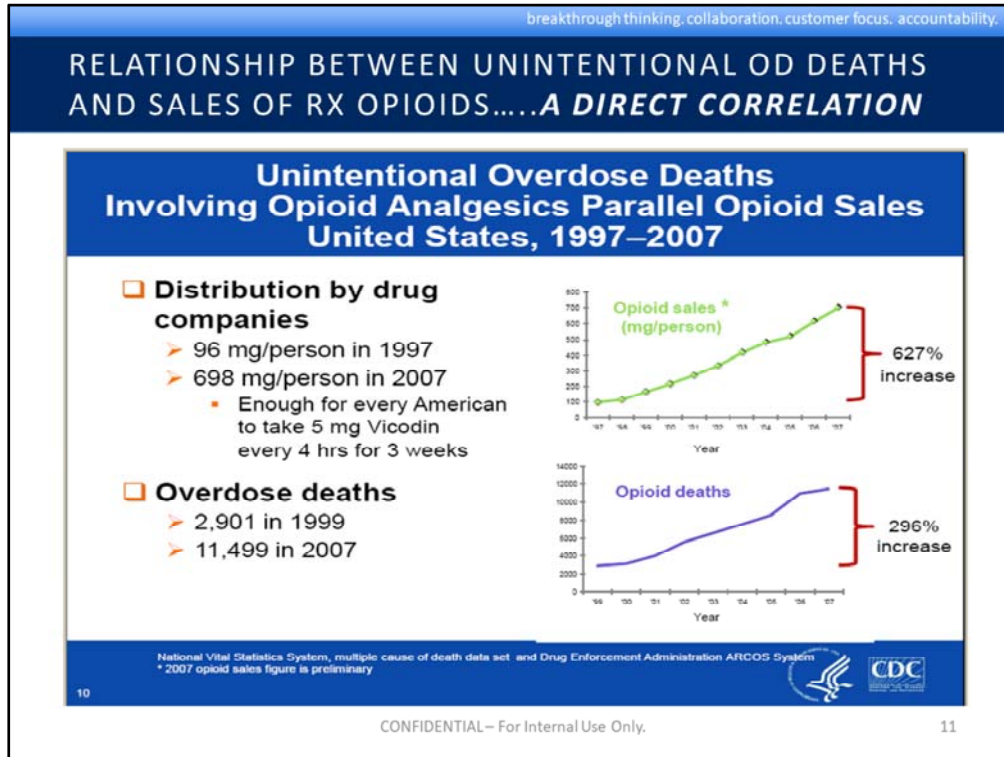
### *SUMMARY OF THE PUBLIC HEALTH CONUNDRUM*

- Both undertreatment of pain & opioid abuse are significant Public Health issues
- ↑ Awareness of need to treat pain has ↑ opioid access & use
- ↑ Opioid access & use has ↑ availability of opioids for misuse
- Rx opioid-related deaths, addiction, abuse & misuse are on the rise
  - Increase has paralleled increase in Rx opioid sales
  - Teens & young adults are fastest growing groups
- > 70% of non-medical users of Rx pain relievers report friends or relatives as the source (2010 SAMHSA)
  - Awareness & educational interventions with prescribers, patients, public can have significant effects

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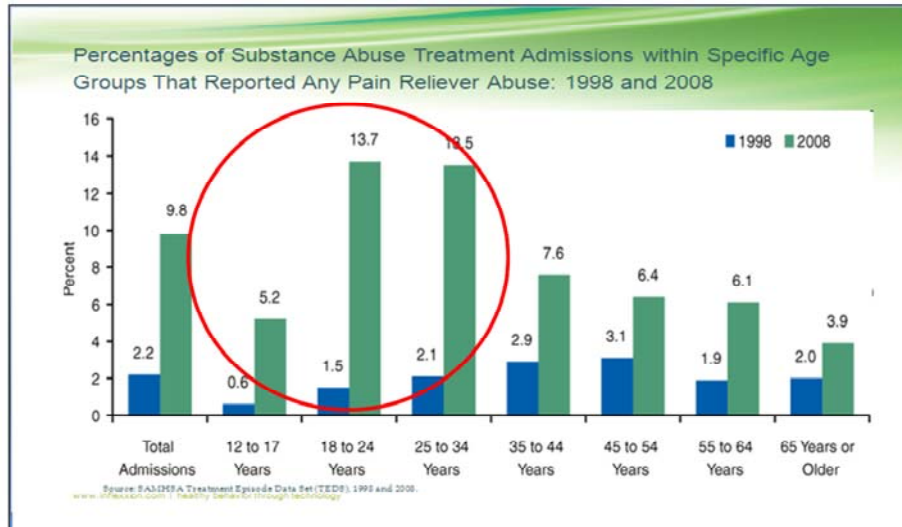
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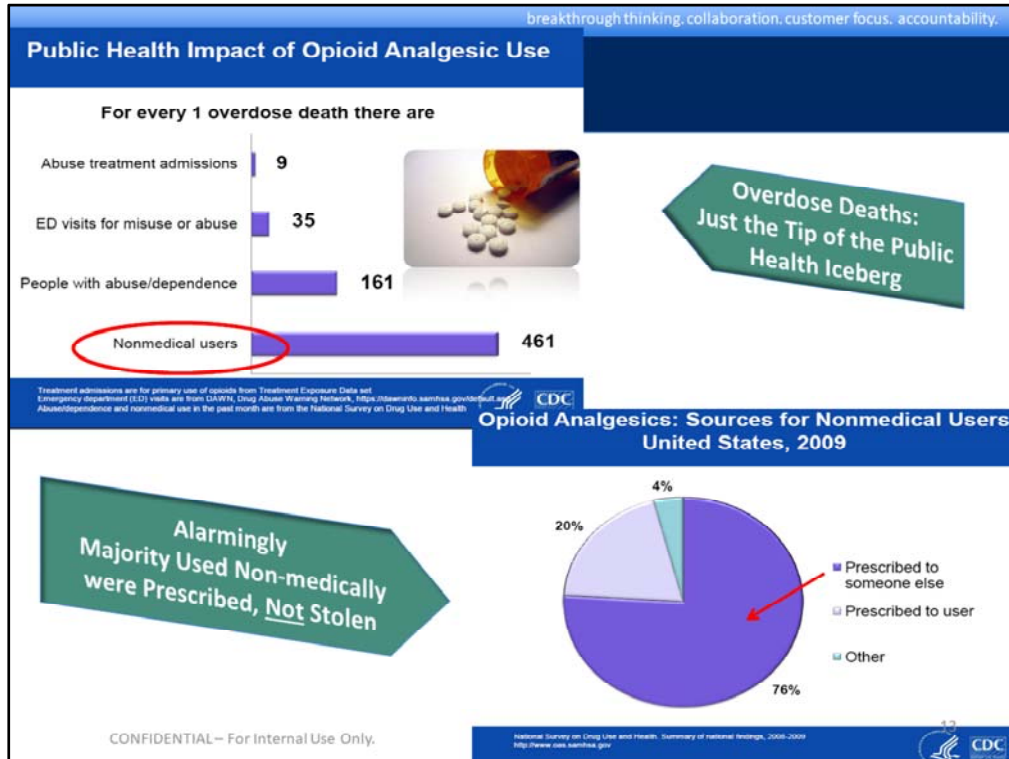
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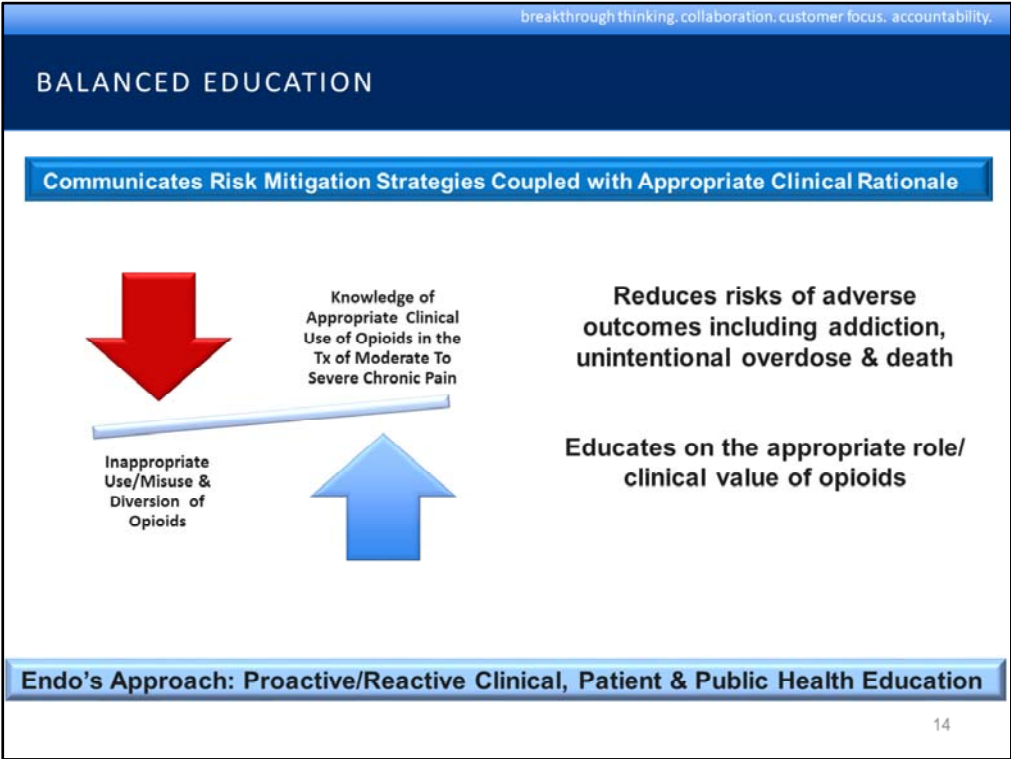
## ABUSE RISING MOST RAPIDLY AMONG TEENS AND YOUNG ADULTS



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| REMS EDUCATION VS “BALANCED” OPIOID EDUCATION (RISKMAP)   |  |
| REMS Education  | “Balanced” Opioid Education  |
| <ul style="list-style-type: none"> <li>• Education to be provided to LA/ER opioid Rx’ers                             <ul style="list-style-type: none"> <li>• CE-accredited</li> <li>• Supported by IWG educational grants</li> </ul> </li> <li>• Focus will be on reducing risks of death, unintentional OD, addiction, abuse &amp; serious AEs</li> <li>• Minimal educational “outcomes” possible because of FDAA limitations</li> <li>• Working closely with ACCME &amp; FDA on:                             <ul style="list-style-type: none"> <li>• National database</li> <li>• Standardized data fields &amp; assessments</li> <li>• Independent audits</li> <li>• Metrics &amp; timeline</li> </ul> </li> <li>• FDA released Draft Blueprint for CE on 11/7                             <ul style="list-style-type: none"> <li>• One month public comment period</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Addresses both aspects of public health issue                             <ul style="list-style-type: none"> <li>• Responsible risk mitigation</li> <li>• Appropriate dx &amp; tx of chronic pain</li> </ul> </li> <li>• Discusses topics not covered by REMS                             <ul style="list-style-type: none"> <li>• Evidence-based guidelines</li> <li>• Role of opioids in chronic pain</li> <li>• Evolving research &amp; data</li> <li>• <math>\mu</math>-opioid receptor variability</li> <li>• Pain in the elderly</li> <li>• Multimodal treatment approaches for                                     <ul style="list-style-type: none"> <li>▪ LBP, OA, NP, etc.</li> </ul> </li> </ul> </li> <li>• Educational outcomes to measure success</li> <li>• All IWG Branded Companies (plus Covidien) plan to continue “balanced” education</li> </ul> |
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## PROBLEM IS MULTIFACTORIAL: RIGHT **PATIENT**...**RIGHT TREATMENT**...**PROPER FOLLOW-UP**

### PROBLEM

Patient Assessment:


- Pain Intensity and Quality
- Relative Risk of Addiction, Abuse, Misuse
- Functionality

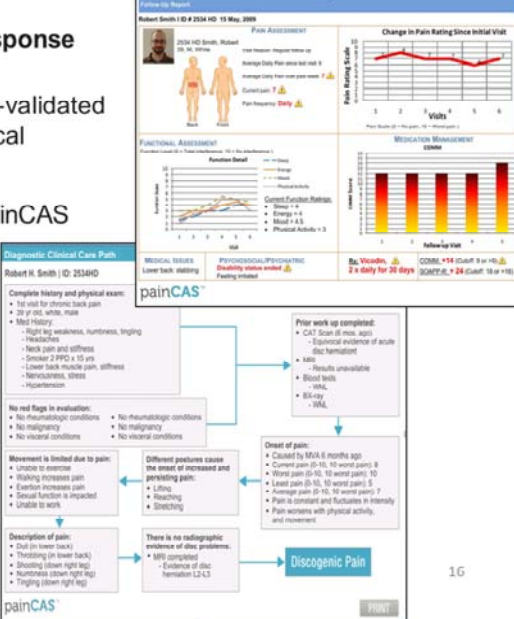


### Current Response

- Psychometrically-validated screeners & clinical resources
- Beta Sites for painCAS
- SOAPP/COMM

**SOAPP/COMM**





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## FACILITATION OF COORDINATED CARE IS CRITICAL ENDO AIMS TO DELIVER TOTAL SOLUTIONS

### PROBLEM


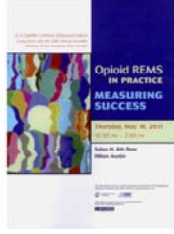
Appropriately  
Managing Chronic  
Pain Patients

Coordinated,  
Multidisciplinary  
Team  
Approach



### Current Response

- Clinical Resources & Education
  - PainEDU.com, painACTION.com, painCAS*
- Resident/Fellow **Annual** Training Program
  - ~1000 trainees over 10 years
- NIPC Live & Enduring
- JAFP/NIPC Podcasts


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## OPIOID MISUSE, ABUSE & ADDICTION ARE SIGNIFICANT PUBLIC HEALTH ISSUES


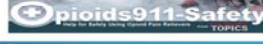

### PROBLEM




**For every 1 overdose deaths there are**

- ✓ 9 Abuse Tx admissions
- ✓ 35 ED visits for misuse or abuse
- ✓ 161 peoples with abuse/dependency
- ✓ 461 nonmedical users

### Current Response

- Appropriate Prescribing Guidelines, Tools & Education 
- Patient/Provider Agreements
- Safe Storage & Disposal Education 
- Partnership for a Drug Free America Initiatives
- NADDI Pilot
- Take-Back Programs 



**Rx Drug Drop Box**

**RxDrugDropBox.org**

The National Association of Drug Diversion Investigators (NADDI) is pleased to announce a brand new grant program for **law enforcement agencies across the country.**



Thanks to Endo Pharmaceuticals, NADDI has obtained funding to provide **100 prescription drug take back boxes** to distribute nationally. ....


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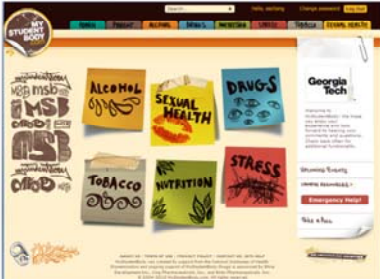
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ENDO SOLUTIONS TO YOUTH & YOUNG ADULT ABUSE/MISUSE/ADDICTION

| PROBLEM  | CURRENT RESPONSE  |
|--|---|
| <div>Rise in Teen and Young Adult Use</div> <div></div> | <div><ul style="list-style-type: none"><li>• Drugs4Real.com</li><li>• MyStudentBody.com</li><li>• National Association of School Nurses Symposium</li><li>• Partnership for a Drug-Free America Activities</li><li>• Support for Recovery High School Initiatives</li></ul></div> <div><div>Intervene</div><div></div><div>Every day, 2500 teens abuse a prescription drug for the first time.</div></div> |





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## SUMMARY


- Misuse & abuse of opioids is a major public health issue
  - Deaths from Rx opioids have reached epidemic levels
  - ~ 12 million Americans (age 12+) reported nonmedical use of Rx opioids in the past year
  - Impacting the problem requires concerted efforts of all stakeholders
- Endo has played a leadership role in IWG Activities
  - Selected as one of 3 major opioid mfgs on Steering Committee
  - Co-chair of Education Sub-team
  - Key roles in Regulatory, Metrics, Patient & Dispenser Sub-teams
  - Integrally involved in FDA/IWG response & negotiations
- Endo is well-positioned to respond to new REMS requirements
- Endo will continue to provide a balanced educational approach
  - Appropriate clinical use of opioids
  - Reduce risks of death, unintentional OD, addiction, misuse & abuse

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July 29, 2019

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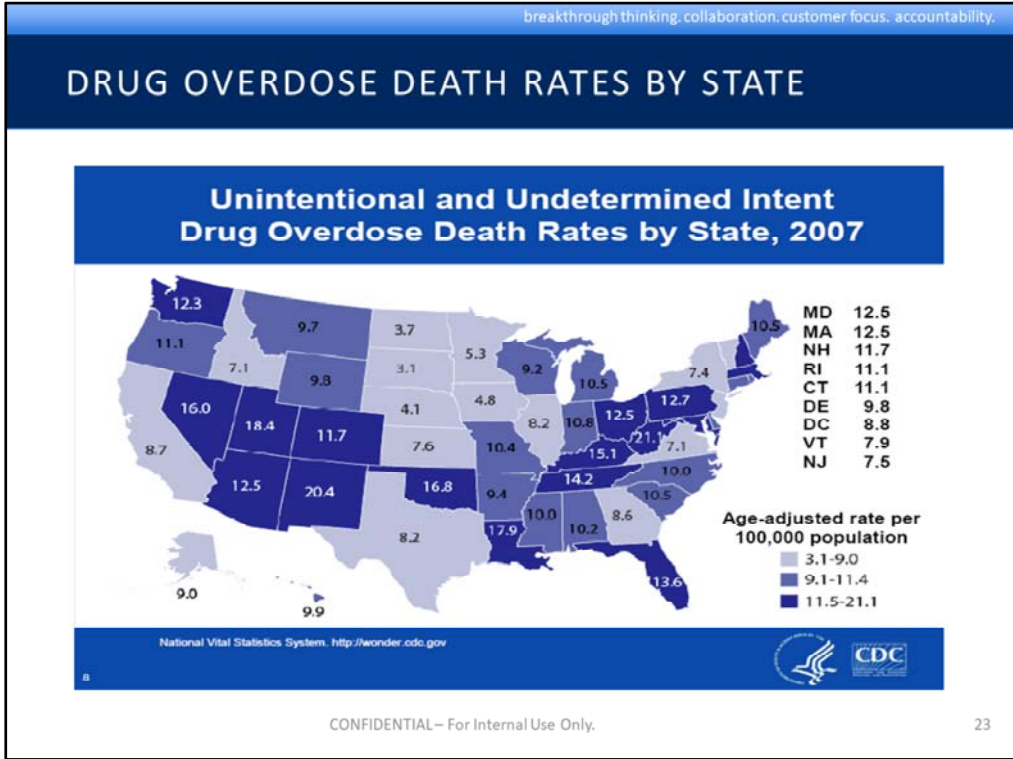
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## BACK UP SLIDES

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## ENDO'S CURRENT PAIN ACTIVITIES: THE OPANA ER RISKMAP – GOALS AND OBJECTIVES

To minimize the following liabilities:

- Aberrant behavior such as drug abuse, misuse, and addiction
  - Among patients
  - In the community, particularly among young adults
- Unintentional drug overdose
- Accidental exposure
- Diversion from distribution/manufacturing facilities
- Improper patient selection
- Fraudulent prescription activity
- Inadequate patient education

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## Endo: Differentiation & Leadership

- As branded & generic provider, uniquely positioned for REMS
- Long-standing leader & supporter of cutting-edge initiatives to support providers with abuse/misuse problem through the development of:

| Awareness Activities  | Educational Resources  | Patient Management Tools  | Community & Public Health   |
|---|--|---|---|
| <ul style="list-style-type: none"> <li>• Responsible Opioid Prescribing</li> <li>• Drugs4Real.com</li> <li>• Partnership for Drug Free America chart</li> <li>• Opioid 911</li> </ul> | <ul style="list-style-type: none"> <li>• Clinical Guide to Opioid Analgesia</li> <li>• NIPC Live Regional &amp; National Series</li> <li>• Understanding Your Pain Brochure Series w/ JCAHO endorsement</li> <li>• PainEdu site &amp; Manual</li> <li>• Primary Care Opioid Handbook</li> <li>• MyStudentBody.com</li> <li>• Veterans in Pain Initiatives (VIP)</li> <li>• NIH Medline Plus Publication</li> </ul> | <ul style="list-style-type: none"> <li>• SOAPP</li> <li>• COMM</li> <li>• painACTION</li> <li>• painCAS</li> <li>• PainSAFE</li> <li>• Patient Action Steps Series</li> <li>• APF &amp; ACPA Resources</li> </ul> | <ul style="list-style-type: none"> <li>• NADDI Pilot</li> <li>• NASCSA Initiatives</li> <li>• DEA Takeback Activities</li> <li>• National Association of School Nurses Education</li> <li>• Drugs4Real.com</li> </ul> |

Continue to partner on innovative programs to lead community outreach efforts

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NADDI take back pilot was brought up at a meeting on Tuesday by the Executive Director of NADDI (National Association of Drug Diversion Investigators). They are hoping to place mailbox type receptacles in police departments to serve as drop-off points for unneeded medications. Looking for a sponsor, Initial cost \$70K.

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## ENDO'S CURRENT PAIN ACTIVITIES: THE OPANA ER RISKMAP – TOOLS

- Product labeling
- Education
  - Professional education initiatives
  - Patient and family
  - Development of new clinically useful validated tools
  - Sales force training
- Tamper-resistant prescription pads
  - Discontinued
- Oversight of the distribution chain
- Postmarketing surveillance

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